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The double-edged sword of AI in Oral Pathology: Opportunities and obstacles

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Abstract

In modern clinical practice, digital pathology plays a crucial role and is increasingly a technological requirement in the laboratory environment. The advent of whole slide imaging, the availability of faster networks, and cheaper storage solutions make it easier for pathologists to manage digital slide images and share them for clinical use.

In this review, we seek to demonstrate the deep learning systems: their potential to function on par with humans in classifying images into diagnostic categories; some of the AI software used in evaluating histopathology images; the significance of AI in evaluating oral mucosal lesions using dermoscopy; challenges and opportunities of AI in digital pathology.

In the present era of AI, the use of these new technologies will assist and place the oral pathologist in a better position to make an accurate diagnosis.

Keywords: Artificial Intelligence (AI), deep learning, whole slide image (WSI), AI software, dermoscopy, potential malignant disorder (PMD)

Introduction

In the current era, artificial intelligence (AI) stands out as one of the most prominent topics of discussion. Recent years have witnessed numerous innovations and advancements that were once confined to the realm of science fiction, now gradually becoming tangible realities. This transformation is achieved through the examination of human brain patterns and the analysis of cognitive processes. The results of these investigations have led to the creation of sophisticated software and systems. The term AI was first coined by John McCarthy in 1956 [1].

AI is a method of making a computer-controlled robot or software that can think and act like a human mind. AI is classified into 3 forms,

1. **Weak/narrow AI:** AI is designed to perform specific tasks and is limited to those tasks only—for example, voice assistants like Siri and Alexa.

2. **Strong/General AI:** where all medical and dental research is going. It is a form that possesses human-level intelligence or may even surpass human intelligence. They focus on training artificial neural networks (ANN) [2].

3. **Super AI:** a form capable of surpassing human intelligence. An example is Dr. Fill, which is a successful AI robot developed by Mathew Ginsberg. It is a computer program that solves American-style crossword puzzles. It has been described by Ginsberg in an article in the Journal of Artificial Intelligence. Dr. Fill started to participate in American crossword puzzle tournaments from 2012 to 2021, where every year the score was seen to be improving from the previous year's score. In 2021 Dr. Fill won the main event scoring 12825 points with Erik Agard, the highest scoring human, scoring 12810 points [3].

The two components of AI software are,

1. Machine learning is centered on creating algorithms and models that allow computers to learn from the data provided to them, enabling them to make predictions or decisions based on existing information.
2. Deep learning serves as a crucial foundation in artificial intelligence, representing a specialized area within machine learning. It emphasizes the training of artificial neural networks that are modeled after the human brain, allowing AI to replicate the brain's neural processes. This capability enables AI to interpret patterns, manage noise, and clarify ambiguities present in the data [2, 4].

How does an AI work?

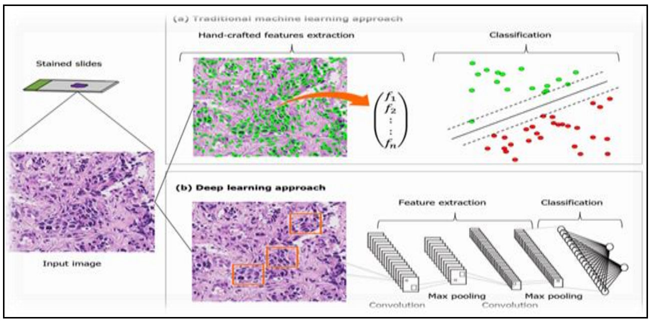

Fig 1: Illustration of an AI system. (Adopted from: World J Gastroenterol 2021; 27(21): 2818–2833).

Consider an image shown in Fig 1, it depicts 3 main layers of a neural network namely:

- **Input Layer:** The image intended for segmentation is introduced into the input layer. It is initially divided into thousands of pixels, with each pixel corresponding to a dot in the input layer.
- **Hidden Layer:** This layer, which has been pre-trained, is tasked with performing all mathematical calculations and extracting features from the input layer.

- **Output Layer:** Ultimately, the output layer processes all the analyzed data and provides the final result [4].

Development of AI-aided computational Pathology

Oral and maxillofacial pathology encompasses a wide array of diseases and conditions that impact the oral cavity, jaws, and facial structures. Effectively diagnosing and managing these conditions necessitates a comprehensive understanding of their underlying causes, clinical manifestations, and histopathological characteristics. However, achieving an accurate diagnosis can be difficult due to the complexity and variability inherent in many oral and maxillofacial pathologies, as well as the potential for discrepancies among pathologists, both between and within observers. To mitigate these challenges, artificial intelligence (AI) software can play a supportive role [5].

For AI to assist oral pathologists effectively, it requires the use of high-quality Whole Slide Image (WSI) scanners. These advanced devices scan glass slides and transform them into digital images that can be analyzed using AI software. The preparation of the glass slides for WSI involves several critical steps, including:

- Tissue procurement
- Fixation, processing, and staining
- Digitization

A procedure is employed to convert high-quality stained slides into complete digital images utilizing advanced whole slide image scanners. Subsequently, these images are analyzed by software in collaboration with a pathologist. This advancement has introduced several new challenges for automated analysis. Pathologists need to ensure that the slides intended for scanning are devoid of any artifacts. The presence of such artifacts may result in certain areas being overlooked by AI software [7].

The main artifacts detected are as shown in Fig 2,

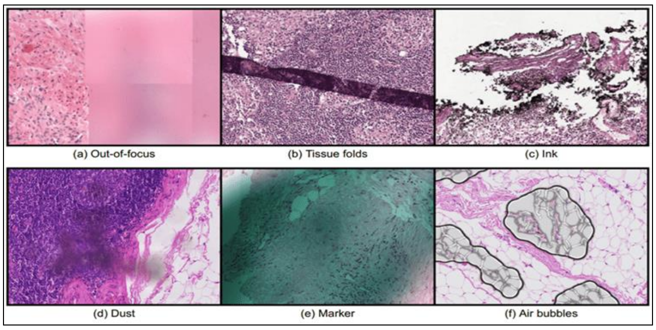

Fig 2: Shows common types of artifacts found in WSI. (Adopted from: Artifact detection in digitized histopathology imageshttps://github.com/DIAGNijmegen/pathology-artifact-detection.git).

(a) The image being out of focus, (b) tissue folds, (c) ink, (d) dust, (e) pen marks, and (f) air bubbles. Depending upon the severity of artifacts the tissue regions of importance may become unreadable by AI. A quality control mechanism is needed to ensure that whole slide images scanned by the scanners should be of good quality to be further analyzed by the software [5, 8].

The final output for a histopathology image can be obtained in the form of

a. Tumor classification
b. Lymph node metastasis
c. Prognosis
d. Treatment response [9].

Recent AI-assisted software used in digital pathology

Abdelsamea *et al* in their studies in 2022 have explained some of the software being developed for analyzing histopathology images [7, 9].

1. Halo image software
2. TuPaQ (Tumor Parcellation and Quantification Tool)
3. DeTraC (Decompose Transfer and Compose)
4. Paige (Paige prostate is the first AI-powered pathology solution to receive FDA approval.)
5. Path

1. Halo image analysis software: The commercially available HALO image analysis software (www.indicalab.com) is used commonly for manual annotations. (Marking around the area of interest).

With the help of this software manually pathologists can mark the invasive tumor complexes in the image (explained in Fig 3) and by using its cytonuclear algorithm in the software, it is possible to segment/divide tumor cell nuclei inside previously classified tumor complexes. But it is time-consuming and might be boring for a pathologist to manually annotate such a large set of images [7, 10].

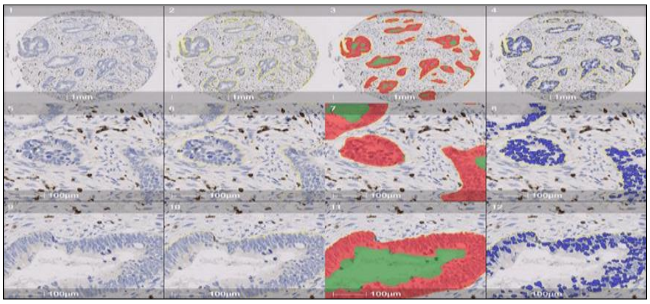

Fig 3: Images 1, 5, and 9 represent scanned TMA images without analysis. The precise manual annotations (yellow line) were drawn to delineate invasive tumor complexes (2, 6, and 10). Images 3, 7, and 11 illustrate HALO image analysis results to classify tumor epithelium (red) inside manual annotations avoiding artifacts (green) such as necrotic debris, stroma, and glandular lumens. HALO Cytonuclear algorithm was calibrated to segment tumor cell nuclei (blue) inside previously classified tumor areas. (Adopted from: A survey on artificial intelligence in histopathology image analysis. WIREs Data Mining and Knowledge Discovery, 12(6), e1474)

(Reference: A survey on artificial intelligence in histopathology image analysis. WIREs Data Mining and Knowledge Discovery, 12(6), e1474)

Trainable methods or classical/statistical machine learning methods, proposed for histopathology image analysis can be classified into two categories, namely, generative and discriminative methods, which mainly consist of 1. Off-line training phase and 2. Online deployment phase.

1. The off-line training phase has the following three steps:

a. Image pre-processing, which aims to diminish the visual variability in the image such as any artifacts mentioned above, and intensity in-homogeneity.
b. Feature extraction, which aims to capture the local characteristics of the data.
c. Description of the feature, which aims to best discriminate (or describe) the features extracted from different segmentation classes [11].

2. The online phase, where the same image pre-processing and feature extraction methods are applied to the unseen image, and then pixel/region-level prediction is done using the trained classifier (or learned probabilistic model) [11].

In short, imaging data may typically be classified in several ways, including structured labels, image annotations, and image segmentation [12].
The main issue that can be considered a significant obstacle to computational pathology is the scarcity of supervised information that has to be provided by professionals to build a supervised deep learning approach, this plays an important role in the final diagnosis of a deep learning model [12].

TuPaQ tool (Tumor Parcellation and Quantification tool)
Is used in analyzing immunohistochemistry stained images (explained by Abdelsamea *et al* in 2019). Here, the first step is to upload WSI scanned image into TuPaQ for automatic image processing. We will get the output in terms of two binary masks for the stroma and epithelium using an active contour model.[7] Then using TuPaQ's tumor epithelium identification (TEI) component the epithelium binary mask is further divided into normal and tumor regions (see fig 4). Finally, we have a Tumor Quantification (TQ) component that is used to divide the nuclei clusters into individual ones and give predicted nuclei counts in the tumor epithelium region [7, 12].

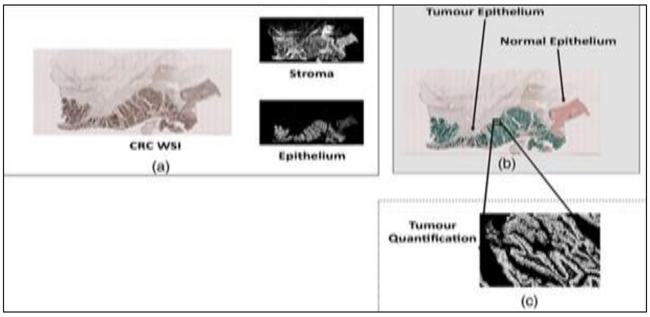

Fig 4: (a). Then the epithelium binary mask is further divided into normal and tumor regions using the TuPaQ's tumor epithelium identification (TEI) component, with the tumor epithelium highlighted in green and the rest of the image in red (b). Finally, a Tumor Quantification (TQ) component is used to divide the nuclei clusters into individual ones and give predicted nuclei counts in the tumor epithelium region (c). (adopted from A survey on artificial intelligence in histopathology image analysis. WIREs Data Mining and Knowledge Discovery, 12(6), e1474).

(Reference: A survey on artificial intelligence in histopathology image analysis. WIREs Data Mining and Knowledge Discovery, 12(6), e1474).

DeTraC (Decompose, Transfer, and Compose (DeTraC) (Abbas *et al*., 2020)
This technique has been proposed to improve the classification performance of histopathological image sections. Designed to cope with data irregularity in image datasets and was used to classify colorectal cancer sections. (See fig 5).
In the software of DeTraC, it has three stages:
In the first stage, a class decomposition method is trained to divide the original dataset into subclasses, resulting in a new dataset (decomposed dataset). Thereby simplify the complexity of the local structure of the original image dataset. (See fig 5)

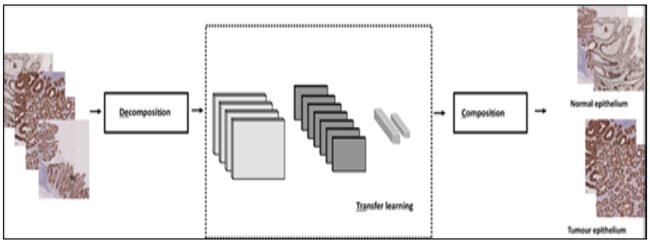

Fig 5: Illustration of DeTraC software. (adopted from A survey on artificial intelligence in histopathology image analysis. WIREs Data Mining and Knowledge Discovery, 12(6), e1474).

(Reference: A survey on artificial intelligence in histopathology image analysis. WIREs Data Mining and Knowledge Discovery, 12(6), e1474).

In the second stage, a pre-trained network is used to read and classify the decomposed dataset. [7] They have found out in their studies that working on the decomposed dataset (instead of the original dataset) can provide the deep learning model with more accurate data and can help in improving them to find out more specialized features. They have concluded their studies by stating that the method can be adopted in any deep learning architecture to cope with complex datasets, especially with the limited availability of training images (as is the case of pathology) [7, 12].

Complexity of histopathology images
Histopathology images are far more complex due to the amount of information contained in the images where several regions are present and each region has a special characterization of its own, in terms of shape, color, texture, gradient, and/or other features. Direct prediction/diagnosis based on visual content, especially microscopic images from histopathology sections, is a challenging task. Many expert pathologists sometimes miss out on major diagnoses hiding within a histopathology image [13].
In Fig 6, a case of dentigerous cyst and odontogenic fibroma has been discussed. Such complex cases where more than one diagnosis can be made within a single image will be a challenge for AI. (See fig 6).

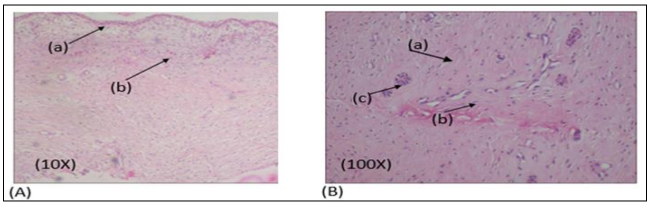

Fig 6: A Case of Dentigerous cyst with Odontogenic Fibroma. (A) Photomicrograph showing cystic wall lined by (a)stratified squamous, nonkeratinized epithelium and composed of (b)fibrous tissue in 10X magnification. (B) Photomicrograph showing (a)mature collagen fibers interspersed with (b)pump fibroblasts and(c) nests of odontogenic epithelium in 40X magnification. (adopted from: Murgod S, Girish HC, Savita JK, Varsha VK. Concurrent central odontogenic fibroma and dentigerous cyst in the maxilla: A rare case report. J Oral Maxillofac Pathol. 2017 Jan-Apr;21(1):149-153. doi: 10.4103/jomfp.JOMFP_33_15. PMID: 28479705; PMCID: PMC5406798.)

(Reference: Murgod S, Girish HC, Savita JK, Varsha VK. Concurrent central odontogenic fibroma and dentigerous cyst in the maxilla: A rare case report. J Oral Maxillofac Pathol. 2017 Jan-Apr;21(1):149-153. doi: 10.4103/jomfp.JOMFP_33_15. PMID: 28479705; PMCID: PMC5406798.)

Schematic representation of digital pathology with analog (traditional pathology). Shown in fig 7

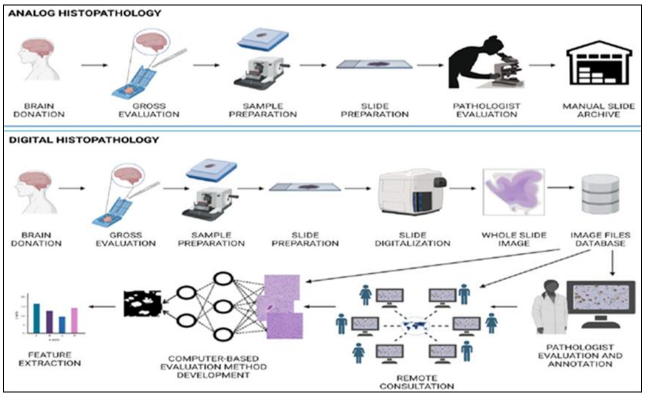

Fig 7: A landscape of the main differences in the workflows of analog and digital histopathology. From whole slide imaging (WSI), image files can be used for various purposes such as diagnosis and annotation, development of tools such as machine learning (ML) algorithms, to assess select features within the image (pathologies, anatomic areas etc.). Experts may use these measures to augment select portions of their annotations/evaluations.

(Reference: John & Chan, Kwun & Dugger, Brittany. (2023). The status of digital pathology and associated infrastructure within Alzheimer's Disease Centers. Journal of Neuropathology and Experimental Neurology. 82. 1-10. 10.1093/jnen/nlac127.)

Dermoscopy for oral mucosal lesions

As a dentist, we also have to think and use this intelligent software in other fields as well so that we can reach out to our patients directly. One such might be AI-assisted dermoscopy. It has been used by dermatologists in the dichotomous image-based discrimination between skin lesions. A similar system and software can be developed for oral lesions which can detect Potential Malignant Disorders (PMD), in its early stage without a need for biopsy. So that treatment can be started and its progression to carcinoma can be reduced. Shagufta rather *et al* in their studies of dermoscopy in oral mucosal lesions have concluded that they can be useful in quick accurate diagnosis. However, there is a need for more studies with a larger sample to better characterize dermoscopic features in oral mucosal disorders and to develop an algorithm for the diagnosis of the same [14, 15].

Where in India?

Many of the labs and hospitals in India have started using this intelligent software. Some of them are listed below.

1. Onward assist, Hyderabad-based lab.
2. Niramai health analystic lab.
3. Digiscan lab, New Delhi.
4. HCG Enterprises Ltd.
5. Tata Memorial Hospital, Mumbai.

Opportunities for AI in digital pathology

1. Pretraining involves training a deep learning network using a substantial collection of images. All histopathology images must be annotated and integrated into AI software as part of the training process for these networks. This process is conducted under the guidance of a pathologist, which will subsequently enhance their relevance in the field.
2. Generative frameworks focus on learning joint probability, which encompasses the statistical characteristics of image features, and predicting labels instead of providing direct conclusions. The software is designed to comprehensively analyze the image before arriving at a diagnosis.
3. The exploration of unsupervised learning algorithms is essential. Pathologists should collaborate with software engineers to create these algorithms effectively.
4. The resurgence of H & E staining has been notable in recent years, particularly with the rise of molecular testing. The integration of computational pathology and advanced 3D technologies allows for a more detailed examination of individual pixels within pathology images.
5. It is crucial for pathologists to ensure that data science tools serve as an asset rather than a liability by enhancing their value, efficiency, and accuracy [16].

Challenges for AI in Digital Pathology

1. High-quality, extensive datasets of trained images are essential for AI, and these images must be manually annotated by pathologists. However, the task of labeling a large volume of images can be tedious and demanding for pathologists.
2. For computer algorithms to effectively interpret histopathology images, the number of patterns derived from fundamental tissue types must be virtually limitless from a computational standpoint. Consequently, the architecture of AI necessitates a substantial number of training examples.
3. The non-Boolean aspect of digital pathology involves binary variables, presenting only two possible outcomes: benign or malignant. This binary classification significantly oversimplifies the intricate nature of pathological assessments.
4. Whole slide imaging (WSI) encompasses gigapixel images, whereas deep artificial neural networks (ANNs) function on much smaller scales. This discrepancy raises concerns regarding the process of patching, which involves segmenting images into smaller pixels, posing a challenge for AI applications.
5. Financial constraints are a significant concern, as pathology laboratories are already facing considerable pressure to implement WSI technology. The additional requirement for graphical processing units (GPUs) to support advanced AI solutions may further strain their budgets in the future.
6. Despite the enthusiasm surrounding AI, the practical integration of this technology into everyday workflows presents substantial challenges. Considering the various obstacles and opportunities, it is clear that pathologists must play a pivotal role in the development and implementation of algorithms [17].

Conclusion

Digital pathology is transforming disease diagnosis. Histological slides can now be able to view across hospital networks that are telecommunication by which a second opinion is possible. Another benefit is the ability to implement the software to highlight pathological areas of interest on the slide. The recent approvals of WSI scanners for primary diagnosis by the FDA, and approval of the prostate AI algorithm have paved the way for starting to incorporate this exciting technology for use in primary diagnosis. However, the golden standard rule for the final diagnosis should be done with the direct vision of a trained pathologist. Artificial intelligence should be used to help pathologists in their day-to-day activities rather than replace them. Indeed, we cannot change what is there in the future but we can go along with it by having a deep knowledge of every perspective of digital pathology & artificial intelligence.

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